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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,560	02/09/2001	Marianne Harboe	58982.000002	6162

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EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 04/02/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Applicati n N .

09/779,560

Applicant(s)

HARBOE, MARIANNE

Examiner

David J. Steadman

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 March 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) ☐ they raise the issue of new matter (see Note below);
 - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☒ Applicant's reply has overcome the following rejection(s): see attached.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: 1-6,9-18,29-31,35,36 and 39-41.

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
10. ☐ Other: _____

ADVISORY ACTION

[1] Claims 1-6, 9-18, 29-31, 35, 36, and 39-41 are pending in the application.

[2] Claims 1-6, 9-18, 29-31, 35, 36, and 39-41 stand finally rejected.

[3] Applicant's cancellation of claims 7-8, 19-28, 32-34, 37, and 38, amendment to claims 1-3, 6, 13-18, 29, and 31, and addition of claims 40 and 41 in Paper No. 13, filed 03/19/03, is acknowledged.

[4] The request for reconsideration in the after final amendment of Paper No. 13 is acknowledged.

While the amendment is sufficient to overcome some of the previously stated objections and/or rejections, the amendment does not place the claims in condition for allowance for the reasons stated below.

[5] In view of applicant's amendment, the rejection of claims 1, 4-32, and 35-39 under 35 USC 112, second paragraph, is withdrawn.

[6] In view of applicant's amendment, the written description rejection of claim 32 under 35 U.S.C. 112, first paragraph, is withdrawn.

[7] In view of applicant's amendment, the scope of enablement rejection of claims 1-32 and 35-39 under 35 U.S.C. 112, first paragraph, is withdrawn.

[8] It is noted that in view of applicant's amendment to limit the desired enzyme activity to chymosin and undesired enzyme activities to glucoamylase, peptidase, amylase, cellulase, phosphatase, and protease, claims 1-6, 9, 12-18, and 31 now stand rejected under 35 USC 103(a) as being unpatentable over Laustsen (US Patent 6,080,564) in view of Larsen (WO 95/29999), Heinsohn (US Patent 5,215,908), and Ward et al. (*Biotechnol* 8:435-440) as applied to claims 10, 11, 23, 24, 29, 30, 32, 35-37, and 39 in previous Office actions (see item 13 of Paper No. 8 and item 8 of Paper No. 11).

[9] The rejection of claims 1-6, 9-18, 29-31, 35, 36, and 39-41 under 35 U.S.C. 103(a) as being unpatentable over Laustsen (US Patent 6,080,564) in view of Larsen (WO 95/29999), Heinsohn (US Patent 5,215,908), and Ward et al. (*Biotechnol* 8:435-440) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 13 of Paper No. 8).

Applicant (beginning at page 8 of Paper No. 13) cites case law and MPEP § 2142, which address rejections under 35 USC 103(a). Beginning at the top of page 10 of Paper No. 13, applicant argues the cited references fail to teach the range of pH as recited in the claims and actually teach away from the recited range. Addressing the reference of Laustsen, applicant argues Laustsen's method of undesirable protein inactivation occurred at pH 3.5 and 10.7. Applicant argues the divergent pH's as taught by Laustsen does not direct one to inactivate amylase at the lower pH. Applicant argues the teachings of Laustsen are likely to suggest the use of a pH of 10.7 or a pH between 3.5 and 10.7. Applicant argues that, even if one were to use the lower pH as taught by Laustsen, there is no suggestion that a pH between 1.5 and 1.9 should or could be used without deleterious effects on the desired enzyme activity. Applicants' arguments are not found persuasive.

While it is acknowledged that Laustsen does not *specifically* teach the use of a pH range of about 1.5 to about 1.9, the reference does *not* teach away from the recited pH range. The reference of Laustsen clearly teaches the use of a low pH (2.0 or 3.5) for the inactivation of amylase, cellulase, and protease enzymatic activities in a culture medium comprising an acid-stable protein (see Examples 4 and 6-8). Furthermore, one of ordinary skill in the art would not expect a pH range of about 1.5 to about 1.9 to have deleterious effects on chymosin as Larsen teaches the *activation* of chymosin by acid treatment using a pH "in the range of 1.5 to 2.5 including a pH of about 2.0" (page 10, line 25). As Larsen teaches that chymosin is *activated* at this pH, an ordinarily skilled artisan would recognize that a pH treatment "in the range of 1.5 to 2.5 including a pH of about 2.0" as taught by Larsen *could not* inactivate chymosin. Consequently, the pH ranges as recited in claims 1 and 13-16 would be rendered obvious by the combined teachings, particularly those teachings of Larsen.

Applicant argues (beginning at the middle of page 10 of Paper No. 13) Heinsohn is directed to purification and not inactivation of undesired enzyme activities. Applicant argues Heinsohn does not teach using a pH range between about 1.5 and about 1.9. to inactivate undesired side activities. Applicant argues Larsen is directed at the activation of endopeptidases not the elimination of undesired enzyme activities. Applicant argues that, given the wide range of pH's used in the cited references of Laustsen,

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Larsen, and Heinsohn, one would not be motivated to combine the three references to obtain the claimed invention. Applicant argues (beginning at the top of page 11 of Paper No. 13) that Ward does not suggest using a pH below 2.0 and therefore, one must combine Ward with the cited references in order to achieve the desired pH range. Applicant argues that because the cited references of Laustsen, Larsen, and Heinsohn do not provide guidance for the recited pH range, their combination with Ward fails to render the claimed invention obvious. Applicant cites case law and asserts the examiner has done no more than find separate elements of the invention and argue that broad disclosures render the claimed invention obvious. Applicant argues there is no motivation to combine the cited references given their distinctly different purposes with an expectation that they would provide the claimed method and one would not be motivated to practice the method at the recited pH. Applicants cite case law in support of their arguments. Applicant argues that the cited references of Laustsen, Larsen, Heinsohn, and Ward do not teach all limitations of the claims and therefore do not render obvious the claimed invention. Applicant argues the examiner has used impermissible hindsight. Applicant's arguments are not found persuasive.

While applicant's attempt to argue the references individually, it is the *combination* of the references of Laustsen, Larsen, Heinsohn, and Ward that render the claimed invention obvious. The examiner acknowledges that no single individual cited reference teaches all claim limitations. Thus, the rejection is made under 35 USC 103(a) and not 35 USC 102. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The knowledge for practicing the claimed methods was well within the level of an ordinarily skilled artisan. Methods for inactivating undesired enzyme activities – particularly those recited in claim 1 - from an enzyme or enzymes that retain enzymatic activity at acidic pH were *well*

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known in the art at the time of the invention. This is representatively demonstrated by the reference of Laustsen. The ability of chymosin to retain enzymatic activity at low pH was well known in the art at the time of the invention – particularly a pH range of 1.5 to 2.5 as taught by Larsen. This is representatively demonstrated by the references of Heinsohn, Larsen, and Ward. In his method, Laustsen teaches that it is preferred to hold the pH as acidic as possible for a desired enzyme that has an acidic pH optimum. Thus, a skilled artisan would recognize that a medium comprising an expressed chymosin can be exposed to a pH in the range of about 1.5 to about 2.5, based on the teachings of Larsen. Therefore, it would have been obvious to expose a medium comprising an expressed chymosin to a pH of between about 1.5 and about 2.5. Such pH treatment would have a variety of benefits including: inactivating undesired enzyme activities as taught by Laustsen, generating mature chymosin from a glucoamylase-chymosin fusion protein as taught by Ward, and stopping the fermentation and growth of cultured *Aspergillus* cells as taught by Heinsohn, all in a single step. Clearly, the benefits obtained in a single step of treating a medium comprising chymosin with a pH of between 1.5 and 2.5 would have motivated an ordinarily skilled artisan to practice the claimed invention. Thus, as the cited references teach all limitations of the claims, provide motivation for practicing the claimed invention, and provide a reasonable expectation of success for practicing the claimed invention as described above, the invention is rendered obvious by the cited references.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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